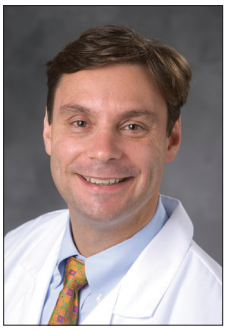
Breakthroughs in Cancer Care



On rare occasions, we witness a true breakthrough in the treatment of cancer. I remember when Druker and colleagues published their phase 1 results with imatinib mesylate for CML in *The New England Journal of Medicine* on April 5, 2001. In their report on efficacy and safety, 53 of 54 patients treated with 300 mg a day had a hematologic complete response, with 29 of these patients demonstrating a cytogenetic response and 7 undergoing complete cytogenetic remission. Just 35 days later, the FDA granted accelerated approval to the drug known as Gleevec, and the outlook for patients with CML was changed overnight. When *Time* magazine featured Gleevec on the cover of its May 28, 2001 issue, I remember feeling proud to be an oncologist. What I didn't know, because I didn't treat CML patients, is what it felt like to offer my own patients a treatment that represented a dramatic improvement in effectiveness.

There have been so many breakthroughs over the last 20 years that sometimes it is difficult to recognize when something monumental occurs. In this era of precision medicine, we have witnessed numerous examples of high response rates and durable remissions within a genetically defined subpopulation of a certain cancer. These targeted approaches are incredibly impactful for selected patients. Unfortunately, they tend to result in only a small improvement for the entire population of patients with that type of cancer. These more common breakthroughs should not obscure those rare occasions when we witness a monumental breakthrough for an entire cancer population—not just a subset, and not just an incremental improvement in outcome.

I'm guessing that most of us didn't attend the 2023 ESMO congress, which took place from October 20 to 24 in Madrid. If so, you may have also missed what is perhaps the greatest single improvement in overall survival by a drug regimen in the first-line setting of a common cancer. Dr Thomas Powles presented the results of EV-302/KEYNOTE-A39, a phase 3 study of enfortumab vedotin (Padvec) and pembrolizumab (Keytruda) vs platinum and gemcitabine chemotherapy for patients with untreated metastatic urothelial cancer (LBA6). For context, platinum-based chemotherapy has been the standard of care for the treatment of metastatic urothelial cancer for the past 30 years, with a stubbornly stable median overall survival of 16 months. The EV-302 study demonstrated a doubling of overall survival for patients receiving Padvec and Keytruda vs chemotherapy (median survival of 31.5 vs 16.1 months, respectively; HR, 0.47; $P<.001$), and a more than doubling of the complete response rate (29.1% vs 12.5%, respectively). The presentation received a standing ovation at the meeting and has received tremendous support within the genitourinary medical oncology community. But otherwise, the experience was quite different from that of Gleevec in CML.

There was no *Time* magazine cover story. There's been little coverage of this study outside of our medical and trade press. There was no FDA approval immediately following these results and the results have not yet been published in a peer-reviewed journal, so I expect our guidelines to be slow to incorporate them. I hope these shortcomings will be rectified by the time of this publication, but as I write this piece, I am facing the challenge of managing a patient in this exact scenario.

Recently, I saw a woman with newly diagnosed metastatic urothelial cancer who is an ideal candidate for this regimen. The problem is that without a new FDA indication or updated guidelines, I might not get this approved through her insurance. I will try, but what if it is denied? She would receive a treatment approach associated with half the survival rate of this denied regimen. There is something wrong with our system if we can no longer act with the kind of immediacy we did with Gleevec and CML.

In 2023, there were an estimated 86,760 new diagnoses of bladder and ureter cancer and 12,760 deaths from these cancers in the United States, according to the most recent statistics from the American Cancer Society. I estimate that for each month that passes until the treatment guidelines change, another 750 or more patients will be diagnosed with metastatic urothelial cancer and will be in the same situation as my patient. We need a more expedited approval process. In the meantime, it is incumbent upon oncologists to make the case for insurance approval, one patient at a time. I am proud, as an oncologist, to advocate on the right side of these appeals. I hope you share the same sentiment.

Sincerely,

Daniel J. George, MD